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ORIGINAL ARTICLE

The serologic decoy receptor 3 (DcR3) levels are associated with slower disease progression in HIV-1/AIDS patients☆

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KEYWORDS
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Background/Purpose: The decoy receptor 3 (DcR3) is a member of the tumor necrosis factor receptor (TNFR) super-family. It counteracts the biological effects of Fas ligands and inhibits apoptosis. The goals of this study were to understand the associations between serologic DcR3 (sDcR3) levels and different human immunodeficiency virus type 1 (HIV-1) subtypes, as well as the AIDS disease progression.
Methods: Serum samples from 61 HIV/AIDS patients, who had been followed up every 6 months for 3 years, were collected. sDcR3 levels were quantified using an enzyme immunoassay (EIA).
Results: The sDcR3 levels in patients with HIV-1 subtype B were significantly higher than those in patients infected with subtype CRF01_AE ($p < 0.001$). In addition, multivariable linear mixed model analysis demonstrated that HIV-1 subtype B and slow disease progression were associated with higher levels of sDcR3, adjusting for potential predictors ($p = 0.0008$ and 0.0455, respectively).
Conclusion: HIV-1-infected cells may gain a survival advantage by activating DcR3, which prevents infected cell detection by the host immune system. These data indicate that the sDcR3 level is a biomarker for AIDS disease progression.

Introduction

The human immunodeficiency virus type 1 (HIV-1) causes AIDS and is one of the leading causes of mortality worldwide.[1,2] HIV-1-infected individuals have revealed that gradual CD4+ T cell depletion takes place in mucosal tissues and peripheral blood during chronic infection.[3–5] Apoptosis is thought to occur in HIV-infected individuals and may arise from mechanisms including HIV-induced syncytium formation, HIV protein-induced cell death, activation-induced cell death, and bystander cell killing.[6–9] The course of HIV infection varies widely among individuals. The median time from infection to development of AIDS is 8–10 years, but a small proportion of patients, probably no more than 5–10%, have been characterized as long-term nonprogressors.[10,11] In contrast, perhaps 10% of all HIV-infected persons are rapid progressors, who develop AIDS within 5 years of infection with HIV.[12,13] The course of HIV infection varies widely among individuals. The interaction of numerous viral and host factors, such as viral virulence, host genetics, host immune response, and cytokine milieu, is believed to determine the course of disease.

Members of the tumor necrosis factor receptor (TNFR) superfamily mediate pleiotropic biological processes, such as cell proliferation, differentiation, apoptosis and cytokine production. DcR3, also known as TR6 or M68, is a new secreted member of the TNFR superfamily and can block the cellular effects by binding to ligands of the TNF family, including Fas ligand (FasL), LIGHT, and TNF-like molecule 1A (TL1A).[14–16] FasL induces apoptosis in target cells through the death receptor Fas and it is reported that DcR3 can prevent FasL-mediated apoptosis.[14,17] Overexpression of DcR3 has been reported in many cancers,[18–21] and systemic lupus erythematous (SLE) patients,[22] and is associated with poor prognoses.[23] A recent study demonstrates that DcR3 expression might be a prognostic marker in various cancers.[23–25] Furthermore, the elevated levels of soluble DcR3 in the sera of patients with gastric, liver, and gallbladder carcinomas, bacterial infection and renal failure, have also been reported.[26–28] Therefore, it is suggested that DcR3 may produce a relative advantage for tumor growth and survival. In animal models, DcR3 is shown to be effective at attenuating FasL-induced mortality and acute pulmonary inflammation.[29,30] Transgenic overexpression of DcR3 is also shown to play a protective role in a rodent diabetic model.[31] DcR3 is also reported to modulate a variety of immune responses. Infiltration of $CD4^+$ and $CD8^+$ T cells, as well as microglia/macrophages, into gliomas, is suppressed by DcR3.[21] When human T cells are pretreated with DcR3, it is found that T cell chemotaxis is inhibited *in vitro* and *in vivo*.[32] Recombinant DcR3 is also shown to downregulate cytotoxic T lymphocyte (CTL) activities to alloantigens and to modulate lymphokine production.[33] Additionally, exogenous DcR3 was reported to modulate dendritic cells (DCs) differentiation and maturation from $CD14^+$ monocytes and these skewed naïve T cells toward a T helper cell type 2 (Th2) phenotype.[34] This suggests that DcR3 might have potent, suppressive effects in downregulation of the host immune system. All the evidence suggested the possibility that DcR3 might be one of the factors responsible for the progression and immune evasion of cancer cells.

Materials and methods

Participants

We used specimens and data from the AIDS Prevention and Research Centre, National Yang-Ming University to investigate the associations between sDcR3 and different HIV-1 subtypes, as well as the AIDS disease progression. A total of 61 HIV-1-infected patients who provided 686 serum samples, with 4–17 visits/patient, were enrolled in this follow-up study from 2000 through 2002. Among 61 HIV-1 infected patients, 50 (82%) were male and the median age was 36 years (range = 19–60 years). In addition, all of the patients were receiving antiretroviral therapy. For each HIV-1 patient included in this study, the day of diagnosis was considered as time zero of the analysis. After the date of diagnosis, HIV-1 patients whose $CD4^+$ T lymphocyte counts

quickly decreased to <200 cells/μL within 3 years, were termed fast progressors. HIV-1 patients whose $CD4^+$ T lymphocyte counts remained at >200 cells/μL within 3 years after the date of diagnosis and declined gradually after 3 years, were termed typical progressors. From the date of diagnosis to 2003, HIV-1 patients whose $CD4^+$ T lymphocyte counts maintained at >500 cells/μL were termed slow progressors. HIV-1 subtypes were determined using polymerase chain reaction (PCR) and phylogenetic analysis.[35] In addition, 145 normal adults who had undergone a physical examination from Kaohsiung Yuan's General Hospital and the Renai branch of Taipei City Hospital, were recruited from 2000 to 2004. All of the normal controls were HIV-1 seronegative. Adults with abnormal GOT and GPT levels (>40 U/L), abnormal platelet levels ($>400 \times 10^3/\mu L$), abnormal carcinoembryonic antigen (CEA) levels (>4 ng/mL), or HBV and HCV infection, were excluded from the control group. Men with abnormal results of clinical prostate examination and women with abnormal results of clinical breast examination, or cervical smear tests, were also excluded from the control group. Informed consent was obtained from all participants in this study and the study was approved by the Institutional Review Board of the National Yang-Ming University.

Serological testing

To measure sDcR3 in HIV-infected patients and the control group, sandwich ELISA was used, containing 9A10C3 and 3H5 monoclonal antibodies. Briefly, each sample was incubated in duplicate in microplates coated with 9A10C3 overnight. Following incubation, the biotin-conjugate 3H5 monoclonal antibody was added and incubated as a primary antibody for 2 hours. After the microplate had been washed, streptavidin-alkaline phosphatase (SA-AKP) (Sigma Co., St. Louis, MO) was added and incubated for 2 hours. After washing off any unbound SA-AKP, *p*-nitrophenyl phosphate (pNPP) (Sigma) was added as a substrate, and the absorbance was measured at 405 nm after 20 minutes with an ELISA reader. The absorbance of each sample was plotted against a standard curve produced by serial dilutions of recombinant DcR3 protein. The amount of DcR3 in the serum samples was determined by extrapolation using calibration curves. The sensitivity limit of the ELISA was 1 ng/mL. All samples with an absorbance of less than the average of the negative control plus two standard deviations (SD), were considered as nondetectable.

Statistical analysis

Univariate analysis was performed using either the Pearson χ^2 test or the Fisher's exact test, as appropriate in comparing the proportions of HIV-1-seropositive subtypes between males and females. Mann-Whitney-Wilcoxon (MWW) Test was used to compare the virus-associated factors, physiological values, and sDcR3 concentrations between male and female individuals from the HIV-1-seropositive groups. The Kruskal-Wallis One Way Test was conducted to compare the sDcR3 concentrations between different disease progressors. A multivariable linear mixed model was performed to identify factors associated with higher levels of sDcR3. SAS statistic software (SAS version 9.1; SAS Institute, Cary, NC, USA) was used for all analyses. Statistical significance was set at $p < 0.05$.

Results

Characteristics of HIV-1-infected patients and normal controls

The characteristics of the HIV-1-infected patients and control group included in this study are shown in Table 1. Among HIV-1-infected patients, the age of males ($n = 50$; 33 ± 1.5 years) was significantly higher than that of females ($n = 11$; 24 ± 2.0 years) (MWW Test, $p = 0.003$). The

Table 1 Characteristics of HIV-1-infected patients and normal controls included in the study.

	HIV-1 infected population			Normal
	Male (%) ($n = 50$)	Female (%) ($n = 11$)	Total (%) ($n = 61$)	Total (%) ($n = 145$)
Age (y)				
<30	17 (34.0)	9 (81.8)	26 (42.6)	26 (17.9)
30–39	17 (34.0)	1 (9.1)	18 (29.5)	69 (47.6)
40–49	12 (24.0)	1 (9.1)	13 (21.3)	49 (33.8)
>50	4 (8.0)	0 (0)	4 (6.6)	1 (0.7)
Median + SE (range)	33 ± 1.5 (19–60)	24 ± 2.0 (19–42)	32 ± 1.3 (19–60)	36 ± 0.5 (22–51)
Subtype				
Subtype B	39 (78.0)	4 (36.4)	43 (70.5)	–
CRF01_AE	11 (22.0)	7 (63.6)	18 (29.5)	–
Progressors				
Fast progressor	21 (42.0)	2 (18.2)	23 (37.7)	–
Typical progressor	19 (38.0)	6 (54.5)	25 (41.0)	–
Slow progressor	10 (20.0)	3 (27.3)	13 (21.3)	–
CD4 (cells/mm^3)	400 ± 13.0	540 ± 30.4	440 ± 12.1	–
CD8 (cells/mm^3)	955 ± 20.5	845 ± 39.3	930 ± 18.5	–
Viral load	0.5 ± 6.2	0.5 ± 41.5	0.5 ± 5.6	–

majority of the male patients with HIV-1/AIDS were infected with subtype B [39/50 (78.0%)]; in contrast, almost the female patients were infected with CRF01_AE [7/11 (63.6%)] (Fisher's exact test, $p = 0.011$). A larger percentage of male than female patients belonged to fast disease progressors (42.0% vs. 18.2%), while almost half of the female patients belonged to typical disease progressors (χ^2 test, $p = 0.32$). We observed that virus-associated factors were significantly different in sex between HIV-1-infected patients (MWW Test, $p = 0.001$ for CD4 counts; $p = 0.007$ for CD8 counts; and $p = 0.036$ for viral load), as well as some physiological values (MWW Test, $p < 0.001$ for systolic pressure, diastolic pressure, GOT, and GPT). GOT and GPT levels in the normal population were significantly lower than that in HIV-1-infected patients (Mann-Whitney Rank Sum Test, $p < 0.001$).

Comparison of serologic DcR3 concentrations in HIV-1-infected patients

In total, the majority of 145 normal controls did not have detectable sDcR3 (81% for male and 91% for female). Among 686 serum samples from 61 HIV-1-infected patients, the sDcR3 concentration (median = 0 ng/mL, range = 0—226 ng/mL) was significantly higher than that in samples from the normal population (MWW Test, $p < 0.001$) (Fig. 1A). Among HIV-1-infected patients, the sDcR3 level in patients infected with subtype B ($n = 494$ belong to 43 patients; median = 2 ng/mL, range = 0—226 ng/mL) was significantly higher than that in patients infected with CRF01_AE ($n = 192$ belong to 18 patients; median = 0 ng/mL, range = 0—65.1 ng/mL) (MWW Test, $p < 0.001$). In addition, the sDcR3 in the majority of serum samples from patients infected with CRF01_AE were under the detection limit of the assay (43.5% for subtype B and 78.1% for CRF01_AE). Because the patients in this study did not have equal or consistent follow-ups, the follow-up period was divided into seven 1-year time periods postdiagnosis for analysis. As shown in Fig. 1B, after the day of diagnosis, the sDcR3 in each year in patients infected with subtype B was significantly higher than that in patients infected with CRF01_AE. After the day of diagnosis, the sDcR3 in individuals with slow progression was higher than that in those with fast and typical progression after 5 years postdiagnosis (Kruskal-Wallis One Way Test, $p = 0.07$ for 5 years, $p = 0.02$ for 6 years, and $p = 0.003$ for >6 years postdiagnosis). The detected rates of serum samples in patients with slow and typical progression increased gradually (slope = 9.42 for slow progressors, slope = 5.63 for typical progressors, and slope = −1.4 for fast progressors) (Fig. 1C).

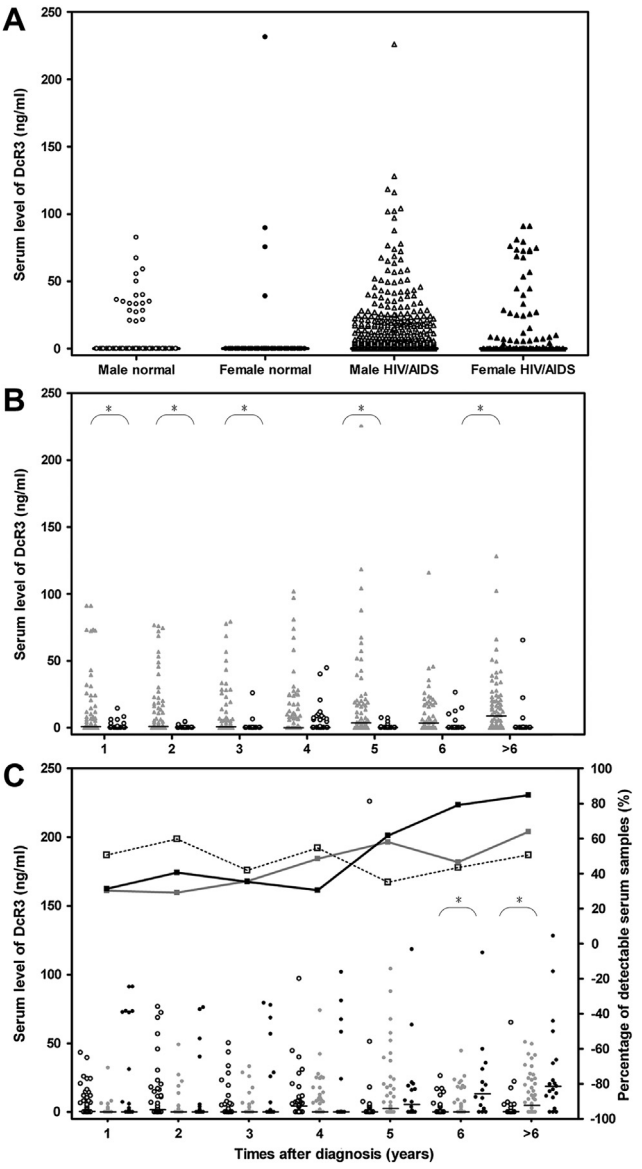

Figure 1 Serologic decoy receptor 3 (sDcR3) in HIV-1-infected patients. Serum samples of HIV-1 patients in multiple time points and normal controls were obtained and sDcR3 were assayed by ELISA in duplicate: (A) sDcR3 of 61 HIV-1-infected patients (50 male and 11 female) and 145 normal controls (100 male and 45 female) were measured; (B) sDcR3 of HIV-1 patients infected with subtype B (gray triangle, $n = 43$) and CRF01_AE (open circle, $n = 18$); (C) sDcR3 of HIV-1 patients belonged to fast progressors (open circle, $n = 23$), typical progressors (gray circle, $n = 25$) and slow progressors (black circle, $n = 13$). The square represents the percentage of detectable serum samples. The dash line indicates the median of sDcR3. The p value was determined by Mann-Whitney Rank Sum Test or Kruskal-Wallis One Way Test. *$p < 0.05$.

Relationship between sDcR3 of HIV-1-infected patients and clinical parameters

Repeated measurements of sDcR3 were analyzed using a linear mixed regression model, accounting for the intra-patient correlation related to AIDS disease progressors over time. To assess the influence of sDcR3 in the HIV-1 patients, we considered the virus-associated factors (i.e., subtypes, viral load, CD4 and CD8 T cell counts) and physiological values (i.e., body temperature, WBC, lymphocyte counts, RBC, systolic pressure, diastolic pressure, GOT, and GPT) over time. In univariate analysis, significantly higher sDcR3 levels were observed in HIV-1 patients with subtype B (B vs. CRF01_AE, $p = 0.0002$), and slow disease progressors (slow vs. typical progressors, $p = 0.0271$; slow vs. fast

Table 2 Multivariate analysis of sDcR3 of HIV-1-infected patients by mixed model.

Variable	Parameter estimate	Standard error	Mixed model, *p*
Intercept	−13.4200	8.4617	0.1183
Times after diagnosis	0.4521	0.4254	0.2883
Age at diagnosis	0.1922	0.1742	0.2705
Sex (male vs. female)	−12.2420	4.8689	0.0122
Subtype (B vs. CRF01_A/E)	13.0089	3.8607	0.0008
CD8 counts	0.0016	0.0022	0.4735
Disease progressions (slow vs. typical + fast)	8.0102	3.9875	0.0450

progressors, $p = 0.0462$) while adjusting sex and age (data not shown). The results suggested that patients who were infected with subtype B and belonged to the slow progressors, had higher sDcR3 levels. In a multivariable linear mixed model, variables were included which were considered to be potentially influential to the concentration of sDcR3 or important confounding variables among HIV-1 infected patients. A mixed model analysis demonstrated that HIV-1 subtype and disease progression led to higher levels of sDcR3 (beta = 13.0089 and 8.0102; $p = 0.0008$ and 0.0450, respectively) (Table 2). The sDcR3 levels of slow progressors infected with subtype B were significantly higher than those in the following three groups: subtype B fast progressors (beta = 10.1168, $p = 0.0211$), CRF01_AE slow progressors (beta = 23.0200, $p = 0.0159$) and CRF01_AE fast progressors (beta = 21.3826, $p < 0.0001$).

Discussion

In the previous study, researchers investigated the amplification and expression of DcR3 in the immune evasion of EBV-associated lymphomas and HTLV-1-associated adult T cell leukemia.[20] DcR3 expression was also induced during the early phase of Kaposi's sarcoma-associated herpesvirus (KSHV) infection.[36] Ho et al demonstrated that EBV can enhance DcR3 through its transcription activator.[37] In the present study, we analyzed the expression of DcR3, using EIA, in HIV-1/AIDS patients and assessed the association of sDcR3 and the disease progression of HIV-1 infection. Our results demonstrate that higher levels of sDcR3 in HIV-1 patients infected with subtype B may slow down the rate of disease progression. HIV-1 uses numerous mechanisms to evade host immune responses, including impairment of HIV-1 specific CD4 and CD8 T-cell function, downregulation of HLA class I molecules, and mutations within defined CTL epitopes.[38–40] The strategies that not only prevent HIV-1 clearance, but also delay the progression to AIDS, in the face of persistent immunity, are still not well understood. It has been assumed that low immune activation found in controllers and long-term nonprogressors, suggests that immune activation forms an important role in the lack of progression.[41] Since TL1A can bind DR3 on immune cells, where this interaction leads to activation and proliferation of lymphocytes and NK cells, it has been speculated that DcR3 might attenuate T-cell activation via its action as a decoy receptor for TL1A.[16] The immune-evasive and Th2-promoting properties of DcR3, might confer benefits to slow down the rate of disease progression by dampening T-cell activation.[42] However, the detailed mechanism of DcR3 contributing to nonprogressors is still to be evaluated. It is possible that HIV-1 uses DcR3 to escape the immune system and confer survival advantage and delay disease progression. This is the first study investigating a possible relationship between sDcR3 and virus-associated factors of patients infected with HIV-1. However, whether an HIV-1 gene regulates DcR3 expression and the role that DcR3 plays in the pathogenesis of HIV-1 infection needs to be elucidated in further studies. In sum, HIV-1-infected cells may gain a survival advantage by activating an immunomodulatory factor, DcR3, which prevents infected cell detection by the host immune system. Further studies to assess the usefulness of serologic DcR3 levels as a biomarker in HIV-1 disease progression will be undertaken.

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